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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/157,289	09/18/98	ASHKENAZI	A 11669.31US03

HM22/0209

DIANE L. MARSCHANG
GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO CA 94080-4990

EXAMINER	
KAUFMAN, C	
ART UNIT	PAPER NUMBER
1646	31

DATE MAILED: 02/09/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/157,289	Applicant(s) ASHKENAZI ET AL.	
	Examiner Claire M. Kaufman	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 1999 and 26 June 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-39,54-56 and 67-88* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *30-39* is/are allowed.

6)☒ Claim(s) *14-23,29,54-56 and 67-88* is/are rejected.

7)☒ Claim(s) *24-28* is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,20-23,26,30*.
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☒ Other: *sequence comparison* .

DETAILED ACTION

The preliminary amendments filed October 19, 1999, and June 26, 2000, have been entered.

Election/Restrictions

Applicant's election of Group II in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Information Disclosure Statement

US Provisional Applications listed in the IDS have been considered, but will not be printed if this application issues as a patent since reference to the applications appears on a PCT and such provisional application are not considered prior art.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It was not executed in accordance with either 37 CFR 1.66 or 1.68.

Inventor Daniel Tumas signed, but did not date the declaration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 72-88 are rejected under 35 U.S.C. 112, first paragraph, because the specification,

while being enabling for A) an antibody which specifically binds DcR3 polypeptide that consists of the amino acid sequence of SEQ ID NO:1 or the extracellular domain thereof consisting of at least amino acid residues 1 to 215 of SEQ ID NO:1, B) an antibody that binds the same epitope as the antibody produced by the hybridoma cell line deposited as ATCC HB-12571-12575, does not reasonably provide enablement for 1) an antibody that binds an DcR3 polypeptide which is not identical to SEQ ID NO:1 (*e.g.*, wherein the polypeptide has a sequence 80% identical to SEQ ID NO:1) or a fragment thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to an antibody that binds a polypeptide that is 80% identical to the extracellular domain SEQ ID NO:1 (DcR3) . The prior art does teach a DcR3 polypeptide (called TR4 by Emery et al., US Patent 5,885,800, and TNFR6α by Gentz et al., WO 98/30694). It also teaches several related polypeptides, for example, DR3 (Marsters et al., Curr. Biol. 6(12), 1996, #120 cited by Applicants, also called TRAMP and Apo-3 in the art) and DR4 (Pan et al., Science 276, 1997, #140 cited by Applicants, also called TRAIL-1 in the art) and DR5 (Marsters et al., Curr. Biol. 6(6), #120 cited by Applicants, also called TRAIL-2 and Apo-2). Also taught is an antibody to DR3 (Marsters et al., #120, see p. 1675, 5th paragraph, and Bodmer et al., Immunity 6, #51, see p.85, 5th paragraph), but that antibody would not be expected to bind DcR3 as the disclosed sequence of DcR3 and DR3 share little identity overall. The prior art does not teach antibodies to the other DR receptors or an actual antibody to DcR3 or an antibody that would reasonably be expected to bind DcR3. It is acknowledged that the skill in the art is high as it relates to the discovery of TNF receptor family proteins, of which DcR3 is a member, but not as it relates to predicting sequences of the receptor proteins or, as a result, the necessary structure of an antibody that would bind an unknown sequence of a member of the receptor

family. Such an unknown sequence is encompassed by the breadth allowed with 80% identity to amino acids 1-215 of SEQ ID NO:1. There is no guidance for using an antibody that does not bind DcR3, which antibody is encompassed by the scope of an antibody that binds a protein 80% identical to SEQ ID NO:1 (DcR3) or the extracellular domain of DcR3. The structure of the antibody would be especially unpredictable for those that not only have to bind the related protein but block an activity of it.

For these reasons, it would require undue experimentation to make the claimed invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-23, 55, 84 and dependent claim 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 55 recites the limitation "DcR3 antibodies of claim 14" in line 3. There is insufficient antecedent basis for this limitation in the claim. Claim 14 recites only a single antibody. Note claim 56 also recites antibodies (plural) and by associates lacks antecedent basis.

Claim 55 is also indefinite because it recites a composition including DcR3 antibodies. However, a composition must have more than one component and it is not clear if the antibodies recited are the important component of the composition. Adding a carrier or other equivalent term with support in the instant specification would obviate this rejection and make it clear that the antibodies are the important part of the composition.

Claim 84 recites the limitation "said mammalian cancer cells" in line 1. There is insufficient antecedent basis for this limitation in the claim. It appears the dependency might have been intended to be from claim 83 instead of 82.

Claims 19-23 are indefinite because it is unclear what "the biological characteristics" are and which characteristics the claimed antibody must have. The specification does not provide a limiting definition (sentence bridging pages 27-28). It is unclear if this means the claimed

antibody must have all biological characteristics, including structure and function, in which case it would have to be identical to the antibody produced by the hybridoma of ATCC HB-12541 (for claim 29), and then the two claims would have the same breadth, or if only some of the characteristics, *e.g.*, certain structural or functional aspects, are meant. Because of this ambiguity, the metes and bounds of the claim are not clear.

Priority

It is also noted that while provisional priority application 60/059,288 discloses the complete DcR3 protein and encoding nucleic acid sequences, it does not disclose a specific utility for the protein. It is disclosed only that the protein is related to TNFR2, but no specific ligand is identified and no actual antibody is taught. Therefore, the instant application is not granted benefit of priority to 60/059,288. For the sake of prior art, the effective filing date of the instant application is that of 60/094,640, filed 07/30/98.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-18, 29, 54-56, 67-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over Emery et al. (US Patent 5,885,800, cited by applicants).

Emery et al. teach the TR4 polypeptide which has a sequence identical to the DcR3 polypeptide (SEQ ID NO:1) of the instant application (see attached COMPARISON TO SEQ ID NO:1). Also taught are methods of making antibodies including antibody (fragments,

monoclonals, polyclonals, recombinant, etc.) and hybridomas to TR4, and the desirability of having such antibodies (col. 10, line 58 to col. 11, line 28). Uses for such antibodies are listed and include affinity chromatography of TR4, treatment of TR4 related diseases including cancer. TR4 is disclosed as structurally related to tumor necrosis factor (TNF) receptors (*e.g.*, col. 6, lines 42-61) for which ligands, including FasL are known (col. 1, lines 31-40).

It would have been obvious to one of skill in the art at the time the invention was made to produce antibodies to TR4 (*a.k.a.*, DcR3) using the well known and routine methods disclosed by Emery et al., for example by establishment of a hybridoma cell line, for the reasons set forth therein such as for the production of antibodies for affinity chromatography of TR4. It further would have been obvious to make an antibody that blocked the binding of the receptor and its ligand as well as an antibody that did not bind related TNF receptors because such receptors and ligand were known to be important in cell death and provide potential specific therapeutics for related diseases. For example, FasL causes lymphoproliferative disease (col. 1, lines 47-53). Note that instructions for using an antibody does not provide patentable weight to an article of manufacture unless the instructions are explicit and provide a novel and unobvious limitation to the claimed article. For these reasons, the invention is *prima facie* obvious.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. WO 98/30694 (#35 cited by applicants) discloses TNFR-6α, which has the same sequence as DcR3 of the instant application and is cumulative with the reference cited above. WO 99/14330 is not prior art, but issued from a PCT claiming priority to the two provisional applications to which the instant US application claims priority.

Term Usage

It is noted that the art also refers to DcR3 as TR4, TR6, TNFR-6alpha, ZTNFR-5, human NTR-1, OPG-2, FLINT#1 and hAPO6.

Conclusion

Claims 30-39 are allowable.

Claims 24-28 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Thursday from 8:30AM to 12:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached at (703) 308-6564.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.

Patent Examiner, Art Unit 1646

February 8, 2001

COMPARISON TO SEQ ID NO:1

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; Sequence 2, Application US/08794796
; Patent No. 5885800
;  GENERAL INFORMATION:
;    APPLICANT:  Emery, John
;    APPLICANT:  Tan, KB
;    APPLICANT:  Truneh, Alem
;    APPLICANT:  Young, Peter
;    TITLE OF INVENTION:  Tumor Necrosis Related Receptor,TR4
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/794,796
;      FILING DATE:  04-FEB-1997
;      CLASSIFICATION:  514
;  INFORMATION FOR SEQ ID NO:  2:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  300 amino acids
;      TYPE:  amino acid
;      STRANDEDNESS:  single
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  protein
US-08-794-796-2


  Query Match             100.0%;  Score 1634;  DB 2;  Length 300;
  Best Local Similarity   100.0%;  Pred. No. 2.1e-127;
  Matches  300;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy       1 MRALEGPGLSLLCLVLALPALLPVPAVRGVAETPTYPWRDAETGERLVCAQCPPGTFVQR 60
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 MRALEGPGLSLLCLVLALPALLPVPAVRGVAETPTYPWRDAETGERLVCAQCPPGTFVQR 60

Qy      61 PCRRDSPTTCGPCPPRHYTQFWNYLERCRYCNVLCGEREEEARACHATHNRACRCRTGFF 120
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      61 PCRRDSPTTCGPCPPRHYTQFWNYLERCRYCNVLCGEREEEARACHATHNRACRCRTGFF 120

Qy     121 AHAGFCLEHASCPPGAGVIAPGTPSQNTQCQPCPPGTFSASSSSSEQCQPHRNCTALGLA 180
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     121 AHAGFCLEHASCPPGAGVIAPGTPSQNTQCQPCPPGTFSASSSSSEQCQPHRNCTALGLA 180

Qy     181 LNVPGSSSHDTLCTSCTGFPLSTRVPGAEECERAVIDFVAFQDISIKRLQRLLQALEAPE 240
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     181 LNVPGSSSHDTLCTSCTGFPLSTRVPGAEECERAVIDFVAFQDISIKRLQRLLQALEAPE 240

Qy     241 GWGPTPRAGRAALQLKLRRRLTELLGAQDGALLVRLLQALRVARMPGLERSVRERFLPVH 300
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db     241 GWGPTPRAGRAALQLKLRRRLTELLGAQDGALLVRLLQALRVARMPGLERSVRERFLPVH 300
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